



Mediation Analysis Without Sequential Ignorability:  
Using Baseline Covariates Interacted with Random  
Assignment as Instrumental Variables

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## Abstract

In randomized trials, researchers are often interested in mediation analysis to understand how a treatment works, in particular how much of a treatment's effect is mediated by an intermediated variable and how much the treatment directly affects the outcome not through the mediator. The standard regression approach to mediation analysis assumes sequential ignorability of the mediator, that is that the mediator is effectively randomly assigned given baseline covariates and the randomized treatment. Since the experiment does not randomize the mediator, sequential ignorability is often not plausible. Ten Have et al. (2007, *Biometrics*), Dunn and Bentall (2007, *Statistics in Medicine*) and Albert (2008, *Statistics in Medicine*) presented methods that use baseline covariates interacted with random assignment as instrumental variables, and do not require sequential ignorability. We make two contributions to this approach. First, in previous work on the instrumental variable approach, it has been assumed that the direct effect of treatment and the effect of the mediator are constant across subjects; we allow for variation in effects across subjects and show what assumptions are needed to obtain consistent estimates for this setting. Second, we develop a method of sensitivity analysis for violations of the key assumption that the direct effect of the treatment and the effect of the mediator do not depend on the baseline covariates.

Keywords: Causal Inference, Mediation Analysis, Instrumental Variables.

## 1. Introduction

Randomized trials are explicitly designed to estimate the effects of treatments but not how those effects occur. Yet, many researchers are interested in how treatments that are evaluated using randomized experiments achieve their effects. Mediation analysis seeks to open up the “black box” of a treatment and explain how it works. For example, the PROSPECT study (Bruce *et al.*, 2004) evaluated an intervention for improving treatment of depression in the elderly in primary care practices. The intervention consisted of having a depression specialist (typically a master’s-level clinician) closely collaborate with the depressed patient and the patient’s primary care physician to facilitate patient and clinician adherence to a treatment algorithm and provide education, support and ongoing assessment to the patient. The intervention significantly reduced depression (as measured by the Hamilton test) four months after baseline. Researchers of this study are interested in to what extent the effect of the intervention can be explained by its increasing use of prescriptive anti-depressant medication as compared to other factors. Understanding the mechanism by which a treatment achieves its effects can help researchers and policymakers design more effective treatments (Gennetian, Bos and Morris, 2002; Kraemer et al., 2002). For example, if the PROSPECT study intervention achieves its effects primarily through increasing use of antidepressants, then a more cost-effective intervention might be designed that has the depression specialist focus her time only on increasing use of antidepressants.

The standard approach to mediation analysis (Judd and Kenny, 1981; Baron and Kenny, 1986; MacKinnon et al., 2002) makes a strong *sequential ignorability* assumption that not only is the intervention randomly assigned, but the mediating variable (e.g., antidepressant) is also ignorable (i.e., there are no unmeasured confounders of the mediating variable-outcome relationship ) given the assigned intervention and measured confounding variables (Ten Have et al., 2007). In the PROSPECT study, potential unmeasured confounders of the mediating variable (antidepressant use)-outcome (depression) relationship include medical comorbidities during the follow-up period, which deter elderly depressed patients from taking antidepressant medications because of so many other medications that are necessitated

by their medical comorbidities and also predisposes patients to more depression (Ten Have et al., 2007). To address such unmeasured confounding, Ten Have et al. (2007) develop an alternative approach to mediation analysis that relies on having a baseline covariate that interacts with random assignment in predicting the mediating variable, but that does not modify the causal effects of the random assignment and the mediating variable. For example, for the PROSPECT study, Ten Have et al. considered the baseline covariates baseline depression and baseline suicide ideation. Ten Have et al.’s approach to mediation analysis uses a rank preserving model for causal effects and  $g$ -estimation (Robins, 1994). The assumption underlying Ten Have et al.’s approach, that there is a baseline covariate that interacts with random assignment in predicting the mediating variable but that does not modify the causal effects of the random assignment and the mediating variable, can be viewed as an assumption that the baseline covariate interacted with random assignment is an instrumental variable (IV) for the mediating variable in a structural equation model. Dunn and Bentall (2007) show that two stage least squares estimation of this structural equation model with the baseline covariate interacted with random assignment as an IV produces essentially equivalent results to that of  $g$ -estimation of the rank preserving model. Gennetian, Bos and Morris (2002), Albert (2008) and Joffe et al. (2008) provide further discussion of this two stage least squares approach.

This paper makes two contributions to the approach of using baseline covariates interacted with random assignment as IVs for mediation analysis when sequential ignorability does not hold. First, in previous work on the instrumental variable approach, it has been assumed that the direct effect of treatment and the effect of the mediator are constant across subjects; we allow for variation in effects across subjects and show what assumptions are needed to obtain consistent estimates for this setting. Second, we develop a method of sensitivity analysis for violations of the key assumption that the direct effect of the treatment and the effect of the mediator do not depend on the baseline covariates.

Our paper is organized as follows. Section 2 provides the notation and setup. Section 3 describes the model we will consider. Section 4 reviews the standard regression approach

to mediation analysis. Section 5 presents the instrumental variables approach. Section 6 develops a method of sensitivity analysis for the effect of departures from the key assumption that the baseline covariate does not modify the causal effects of the random assignment or the mediating variable. The methods are applied to the PROSPECT study. **2. Setup and Notation**

We assume there are  $N$  subjects who are an iid sample from a population. We assume that the treatment  $R$  is randomized.

The observed variables for subject  $i$  are the following:  $Y_i$  is the observed outcome,  $R_i$  is the observed randomized zero-one treatment assignment,  $\mathbf{X}_i$  is a vector of observed baseline covariates other than treatment assignment and  $M_i$  is the observed mediation variable. The potential outcomes for subject  $i$  are  $Y_i^{(r,m)}$ ,  $r = 0$  or  $1$  and  $m \in \mathcal{M}$  where  $\mathcal{M}$  is the set of possible values the mediating variable can take on;  $Y_i^{(r,m)}$  is the outcome variable that would be observed if subject  $i$  were randomized to level  $r$  of the treatment and through some hypothetical mechanism were to receive or exhibit level  $m$  of the mediator. To establish a unique potential outcome, we assume that all such hypothetical mechanisms lead to the same potential outcome (Ten Have et al., 2007). The observed outcome  $Y_i$  is equal to  $Y_i^{(R_i, M_i)}$ . The potential mediating variables for subject  $i$  are  $M_i^{(r)}$ ,  $r = 0$  or  $1$ ;  $M_i^{(r)}$  is the level of the level of the mediating variable that would be observed if subject  $i$  were assigned level  $r$  of the treatment. The observed mediating variable  $M_i$  equals  $M_i^{(R_i)}$ .

We let the random variables  $Y, R, \mathbf{X}, Y^{(r,m)}(r = 0, 1, m \in \mathcal{M}), M^{(r)}(r = 0, 1)$  be the values of the observed outcome, treatment assignment, baseline covariates, potential outcomes and potential mediating variables for a randomly chosen subject from the population.

### 3. Model

We consider the following model for potential outcomes:

$$Y_i^{(r,m)} = Y_i^{(0,0)} + \theta_{M_i} m + \theta_{R_i} r, \quad (1)$$

where the  $(Y_i^{(0,0)}, \theta_{M_i}, \theta_{R_i})$  are iid random vectors. Here  $\theta_{M_i}$  represents the effect for subject  $i$  of a one unit increase in the mediator on the outcome holding the treatment fixed at any

level  $r$ . The parameter  $\theta_{R_i}$  represents the direct effect for subject  $i$  of the treatment on the outcome holding the mediator fixed at any level  $m$ . Let  $\theta_M = E(\theta_{M_i})$  be the average effect of a one unit increase in the mediator and  $\theta_R = E(\theta_{R_i})$  be the average direct effect of the treatment.

#### 4. Review of Standard Regression Approach

The standard regression approach of Baron and Kenny (1986) is to estimate  $\theta_M$  and  $\theta_R$  by least squares regression of  $Y_i$  on  $M_i$  and  $R_i$ . Under the maintained assumption that  $R$  is randomized, the standard regression approach provides consistent estimates of  $\theta_M$  and  $\theta_R$  under the additional assumption that  $M$  is sequentially ignorable given  $R$ :

$$M_i \perp\!\!\!\perp Y_i^{(R_i, m)}, m \in \mathcal{M}, \quad (2)$$

where  $\mathcal{M}$  is the set of possible values of the mediating variable  $M$ . The sequentially ignorable assumption (2) means that  $M$  is effectively randomly assigned given  $R$ . Under model (1), the sequential ignorability assumption (2) is equivalent to

$$M_i \perp\!\!\!\perp Y_i^{(0,0)}, \theta_{M_i}, \theta_{R_i}. \quad (3)$$

See Imai, Keele and Yamamoto (2010) for further discussion of the sequential ignorability assumption. The sequentially ignorable assumption (2) will be violated if there are confounders of the mediator-outcome relationship. Measured baseline confounders of the mediator-outcome relationship can be controlled for by controlling for these confounders in the regression. If there are measured postbaseline confounders, the regression on the measured confounders will produce an unbiased estimate of  $\theta_M$  but not  $\theta_R$ ; to obtain an unbiased estimate of  $\theta_R$ ,  $Y - \hat{\theta}_M$  can be regressed on  $R$  (Vansteelandt, 2009; Ten Have and Joffe, 2010).

#### 5. Instrumental Variables Approach

The standard regression approach can only control for measured confounders of the mediator-outcome relationship. The IV approach using baseline covariates interacted with treatment assignments can control for unmeasured confounders when baseline covariate(s) interacted with treatment assignment are valid IVs. This IV approach for mediation analysis models has been discussed by Dunn and Bentall (2007) and Albert (2008), and the

closely related  $g$ -estimation approach has been discussed by Ten Have et al. (2007). These authors have considered models in which the direct effect of treatment and the effect of the mediating variable are the same for all subjects. We will allow these effect to vary from subject to subject as in (1) and provide conditions needed for the instrumental variable to be consistent.

Denote a vector of baseline covariates by  $\mathbf{X}$ . We assume that the association of  $\mathbf{X}$  with the potential outcomes is linear:

$$E(Y^{(0,0)}|\mathbf{X}) = \alpha + \boldsymbol{\beta}^T \mathbf{X} \quad (4)$$

Then, we can write the observed data  $Y_i$  as

$$\begin{aligned} Y_i &= \boldsymbol{\beta}^T \mathbf{X}_i + \theta_R R_i + \theta_M M_i + \epsilon_i, \\ \epsilon_i &= (\theta_{R_i} - \theta_R) R_i + (\theta_{M_i} - \theta_M) M_i + Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i) \end{aligned} \quad (5)$$

The least squares regression of  $Y$  on  $\mathbf{X}$ ,  $R$  and  $M$  will produce biased estimates if there are unobserved confounders of the mediator-outcome relationship that make  $\epsilon_i$  correlated with  $M_i$ . The method of instrumental variables (IVs) seeks to replace  $M_i$  with its expectation given instrumental variables that help to predict  $M_i$  and are uncorrelated with  $\epsilon_i$ . The interactions between the baseline covariates  $\mathbf{X}$  and  $R$  are valid IVs if the following conditions hold:

- (IV-A1) The interaction between  $R$  and  $\mathbf{X}$  is helpful for predicting  $M$  in a linear model, i.e.,  $E^*(M|R, \mathbf{X}) \neq E^*(M|R, \mathbf{X}, R\mathbf{X})$  where  $E^*(M|\mathbf{A}) = \arg \min_{\boldsymbol{\lambda}} E(M - \boldsymbol{\lambda}^T \mathbf{A})^2$  denotes the best linear predictor of  $M$  given  $\mathbf{A}$ .
- (IV-A2) The average direct effect of the treatment given  $\mathbf{X}$ ,  $E(\theta_{R_i}|\mathbf{X}_i) = \mathbf{X}$ , is the same for all  $\mathbf{X}$ , i.e.,  $E(\theta_{R_i}|\mathbf{X}_i) = \mathbf{X}) = \theta_R$  for all  $\mathbf{X}$ . Likewise, the average effect of the mediating variable given  $\mathbf{X}$ ,  $E(\theta_{M_i}|\mathbf{X}_i = \mathbf{X})$ , is the same for all  $\mathbf{X}$ , i.e.,  $E(\theta_{M_i}|\mathbf{X}_i = \mathbf{X}) = \theta_M$  for all  $\mathbf{X}$ .



(IV-A3) The value of the mediating variable is independent of the effect of the mediating variable given the treatment and the baseline covariates

$$M_i \perp\!\!\!\perp \theta_{M_i} | R_i, \mathbf{X}_i \quad (6)$$

(IV-A1) says that  $R\mathbf{X}$  helps to predict  $M$ . (IV-A2) and (IV-A3), and the assumption that  $R$  is randomly assigned, together guarantee that  $R\mathbf{X}$  is uncorrelated with  $\epsilon_i$ , which we show in the following.

**Proposition 1:** Under (IV-A2) and (IV-A3) and the assumption that  $R$  is randomly assigned, each component of  $R \times \mathbf{X}_i$  is uncorrelated with  $\epsilon_i$ .

**Proof:** Consider a component of  $R \times \mathbf{X}_i$ ,  $RX_{i1}$ . From (5),  $\epsilon_i = (\theta_{R_i} - \theta_R)R_i + (\theta_{M_i} - \theta_M)M_i + \{Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i)\}$ . We will prove that  $Cov(RX_{i1}, \epsilon_i) = 0$  by showing that  $RX_{i1}$  is uncorrelated with each of the three summands that make up  $\epsilon_i$ , namely (i)  $Cov(RX_{i1}, (\theta_{R_i} - \theta_R)R_i) = 0$ ; (ii)  $Cov(RX_{i1}, (\theta_{M_i} - \theta_M)M_i) = 0$  and (iii)  $Cov(RX_{i1}, Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i)) = 0$ . For (i), since  $R_i$  is randomized, we have  $E[(\theta_{R_i} - \theta_R)R_i] = 0$  so that  $Cov(R_iX_{i1}, (\theta_{R_i} - \theta_R)R_i) = E(R_iX_{i1}(\theta_{R_i} - \theta_R)R_i)$ . Furthermore, we have

$$\begin{aligned} E(R_iX_{i1}(\theta_{R_i} - \theta_R)R_i) &= E(R_i^2)E(X_{i1}(\theta_{R_i} - \theta_R)) \\ &= 0, \end{aligned}$$

where the first equality follows from the fact that  $R$  is randomized and the second equality follows from (IV-A2). This proves (i). For (ii), we first note that

$$\begin{aligned} E[(\theta_{M_i} - \theta_M)M_i] &= E[E[(\theta_{M_i} - \theta_M)M_i|R_i, \mathbf{X}_i]] \\ &= E[E[(\theta_{M_i} - \theta_M)|R_i, \mathbf{X}_i]E[M_i|R_i, \mathbf{X}_i]] \\ &= 0, \end{aligned}$$

where the second equality follows from (IV-A3) and the third equality follows from (IV-A2) and the fact that  $R$  is randomized. Thus,  $Cov(R_iX_{i1}, (\theta_{M_i} - \theta_M)M_i) = E(R_iX_{i1}(\theta_{M_i} - \theta_M)M_i) = 0$ .

$\theta_M)M_i)$ , and

$$\begin{aligned}
E(R_i X_{i1}(\theta_{M_i} - \theta_M)M_i) &= E[E[R_i X_{i1}(\theta_{M_i} - \theta_M)M_i | R_i, \mathbf{X}_i]] \\
&= E[R_i X_{i1} E[(\theta_{M_i} - \theta_M)M_i | R_i, \mathbf{X}_i]] \\
&= E[R_i X_{i1} E[(\theta_{M_i} - \theta_M) | R_i, \mathbf{X}_i] E[M_i | R_i, \mathbf{X}_i]] \\
&= 0,
\end{aligned}$$

where the third equality follows from (IV-A3) and the fourth equality follows from (IV-A2) and the fact that  $R$  is randomized. This proves (ii). For (iii),

$$\begin{aligned}
Cov(R_i X_{i1}, Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]) &= E[R_i X_{i1} \{Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]\}] \\
&= E(R_i) E[X_{i1} \{Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]\}] \\
&= 0,
\end{aligned}$$

where the second equality follows from  $R$  being randomized and third equality from properties of conditional expectation. This proves (iii).  $\square$

Assumption (IV-A3) is weaker than the sequential ignorability assumption (2) because (IV-A3) does not say that  $Y_i^{(0,0)}$  is independent of  $M_i$ . Assumption (IV-A3) says that the level of the mediating variable is independent of the effect the mediating variable has, while sequential ignorability says that not only is the level independent of the effect, but also the level is independent of all the person's potential outcomes. In the context of the PROSPECT study, (IV-A3) says that antidepressant use is independent of the effect that the antidepressant would have, while sequential ignorability says that not only is antidepressant use independent of its effect, but antidepressant use is also independent of unmeasured medical comorbidities and any other unmeasured variables that affect depression. Note that (IV-A3) is automatically satisfied if  $\theta_{R_i}$  and  $\theta_{M_i}$  if  $\theta_{R_i}$  and  $\theta_{M_i}$  are the same for all subjects as is assumed by Ten Have et al. (2007), Dunn and Bentall (2007) and Albert (2008).

Under (IV-A2)-(IV-A3), we have

$$\begin{aligned}
E^*(Y | R, \mathbf{X}, R \times \mathbf{X}) &= \alpha + \boldsymbol{\beta}^T \mathbf{X} + \theta_R R + \theta_M E^*(M | R, \mathbf{X}, R \times \mathbf{X}) + E^*(\epsilon | R, \mathbf{X}, R \times \mathbf{X}) \\
&= \alpha + \boldsymbol{\beta}^T \mathbf{X} + \theta_R R + \theta_M E^*(M | R, \mathbf{X}, R \times \mathbf{X}),
\end{aligned}$$

The two-stage least squares estimates of  $\theta_R$  and  $\theta_M$  are found as follows:

1. Regress  $M$  on  $R$ ,  $\mathbf{X}$  and  $R \times \mathbf{X}$  using least squares and obtain the predicted values  $\hat{E}(M|R, \mathbf{X}, R \times \mathbf{X})$ .
2. Regress  $Y$  on  $R$ ,  $\mathbf{X}$  and  $\hat{E}(M|R, \mathbf{X}, R \times \mathbf{X})$  using least squares. The coefficient on  $R$  is  $\hat{\theta}_R$  and the coefficient on  $\hat{E}(M|R, \mathbf{X}, R \times \mathbf{X})$  is  $\hat{\theta}_M$ .

Using the theory of instrumental variables for single-equation linear models (Wooldridge, 2002, Ch. 5), the two stage least squares estimates are consistent under (IV-A1)-(IV-A3) because (i)  $\text{Cov}(R \times \mathbf{X}, \epsilon) = \mathbf{0}$  under (IV-A2)-(IV-A3) and (ii) the coefficient on  $R \times \mathbf{X}$  in the linear projection of  $Y$  onto  $R$ ,  $\mathbf{X}$  and  $R \times \mathbf{X}$  is not  $\mathbf{0}$  under (IV-A1).

We now discuss the variance-covariance matrix of  $\hat{\boldsymbol{\kappa}} = (\hat{\alpha}, \hat{\boldsymbol{\beta}}, \hat{\theta}_R, \hat{\theta}_M)$ . First, consider the following additional assumptions:

- (AA-1) The distribution of the direct effect of the treatment and the effect of the mediating variable do not depend on  $\mathbf{X}_i$ ,

$$\theta_{R,i}, \theta_{M,i} \perp\!\!\!\perp \mathbf{X}_i.$$

- (AA-2)  $\text{Var}(\{Y_i^{(0,0)} - E(Y_i^{(0,0)})\}|\mathbf{X}_i = \mathbf{X})$  is the same for all  $\mathbf{X}$ .

Under (AA-1)-(AA-2), the  $\text{Var}(\epsilon_i|R_i, \mathbf{X}_i)$  is the same for all  $R_i, \mathbf{X}_i$ . Then a consistent estimate of the variance-covariance matrix of  $\hat{\boldsymbol{\kappa}}$  is  $\hat{\sigma}_\epsilon^2(\mathbf{A}^T \mathbf{A})^{-1}$  where  $\hat{\sigma}_\epsilon^2 = \frac{1}{N} \sum_{i=1}^N \hat{\epsilon}_i^2$ ,  $\hat{\epsilon}_i = Y_i - \hat{\alpha} - \hat{\boldsymbol{\beta}}^T \mathbf{X}_i - \hat{\theta}_R R_i - \hat{\theta}_M M_i$  and  $\mathbf{A}$  is a matrix with  $N$  rows consisting of a column of ones, columns for each of the variables in  $\mathbf{X}$  for the  $N$  subjects, a column of the values of  $R$  for the  $N$  subjects and a column of the values of  $\hat{E}^*(M|R, \mathbf{X}, R \times \mathbf{X})$  for the  $N$  subjects (Wooldridge, 2002, Ch. 5). By a consistent estimate of the covariance matrix, we mean that  $\sqrt{N}\hat{Cov}(\hat{\boldsymbol{\kappa}}_N)$  is a consistent estimator of  $\sqrt{N}Cov(\hat{\boldsymbol{\kappa}}_N)$ , where  $\hat{\boldsymbol{\kappa}}_N$  is the two stage least squares estimator of  $\boldsymbol{\kappa}$  based on  $N$  observations.

Suppose that either (a) the  $Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i)$  have a distribution that depends on  $\mathbf{X}_i$ ; and/or (b) the direct effects of treatment and the effect of the mediating variable have a distribution that might depend on  $\mathbf{X}$  but the mean is the same for all  $\mathbf{X}$ , i.e.,  $E(\theta_{R,i}|\mathbf{X}_i) = \theta_R$

and  $E(\theta_{M,i}|\mathbf{X}_i) = \theta_M$ . Then, the two stage least squares estimate remains consistent, but the usual standard error might be inconsistent. A consistent estimate of the covariance matrix under regularity conditions (White, 1982; Wooldridge, 2002, Ch. 5.2.5) is the “sandwich” estimator,  $(\mathbf{A}^T \mathbf{A})^{-1} \left( \sum_{i=1}^N \hat{\epsilon}_i^2 \mathbf{A}_i^T \mathbf{A}_i \right) (\mathbf{A}^T \mathbf{A})^{-1}$ , where  $\mathbf{A}_i = (1, \mathbf{X}_i, R_i, M_i)^T$ .

Inferences from two stage least squares become unreliable if the IV(s) are “weak,” which in our setting means that the interaction between  $R$  and  $\mathbf{X}$  is only a weak predictor of  $M$  in the linear model, i.e.,  $E^*(M|R, \mathbf{X}R\mathbf{X})$ . Specifically, when the IV(s) are weak, the two stage least squares estimates can have a large bias in the direction of the ordinary least squares estimates of  $Y$  on  $\mathbf{X}$ ,  $R$  and  $M$ , and the coverage of the confidence intervals for the two stage least squares estimates can be poor (Bound, Jaeger and Baker, 1995). Stock, Wright and Yogo (2002) provided a criterion for when IV inference is reliable based on the partial  $F$  statistic for testing that the coefficient on the  $R \times \mathbf{X}$  variable are zero from the first stage regression of  $M$  on  $R$ ,  $\mathbf{X}$  and  $R \times \mathbf{X}$ . Inference can be expected to be reliable when this  $F$  statistic is greater than 8.96, 11.59, 12.83, 15.09, 20.88 and 26.80 for 1, 2, 3, 5, 10 and 15 variables in  $\mathbf{X}$  respectively. This criterion is based on the goal of having a nominal 0.05 level test of the coefficient on  $M$  have at most actual level 0.15, and the chance that we falsely say that a nominal 0.05 level test of  $M$  has at most actual level 0.15 be at most 0.05.

### 5.1 Application to PROSPECT study

We use the PROSPECT study data set provided by Ten Have et al. (2007) under the Article Information link at the *Biometrics* website <http://www.tibs.org/biometrics>. There are 297 subjects, 145 were randomized to the intervention and 152 to the control. The outcome is the subject’s Hamilton score (a measure of depression, with a higher score indicating more depression) four months after the intervention. The mediating variable is an indicator for whether the subject used antidepressants during the period from the intervention to four months after the intervention. The intervention significantly increases the mediator – the intervention is estimated to multiply the odds of antidepressant use by 6.7 with a 95% confidence interval of (3.9, 11.7).

The second row of Table 1 shows estimates from the standard regression approach. Base-

line covariates are baseline Hamilton score, a baseline indicator of whether the subject had suicide ideation, the site at which the subject was treated (Cornell, University of Pennsylvania or University of Pittsburgh) an indicator of whether the subject has used antidepressants in the past and a baseline ordinal measure of antidepressant use. The intervention is estimated to have a direct effect of reducing depression and antidepressant use is estimated to reduce depression, with the direct effect being significant but the mediator effect not significant.

Following Ten Have et al. (2007), we consider as instrumental variables the interaction between the randomized intervention and two of the baseline covariates, (i) indicator of whether the subject has used antidepressants in the past and (ii) baseline ordinal measure of antidepressant use. The partial  $F$  statistic for the instruments in the first stage regression is 27.13 indicating that these are not weak instruments. The two stage least squares estimates are shown in the third row of Table 2. The confidence intervals are based on the assumption that the  $\epsilon_i$  are homoskedastic, but the confidence intervals are similar if we use the sandwich covariance estimates that allow for heteroskedasticity.

Method	Direct effect of intervention	Mediator effect
Standard Regression	-2.74 (-0.94, -4.54)	-1.17 (-3.31, 0.97)
IV	-0.94 (-3.92, 2.04)	-2.87 (-8.89, 3.15)

Table 1: Estimates for the direct effect of the intervention and the mediator (antidepressant use) effect in the PROSPECT study. 95% confidence intervals are in parentheses.

## 6. Sensitivity Analysis

In this section, we will consider the sensitivity of inferences to violations of assumption (IV-A2) that the average direct effect of the treatment given  $\mathbf{X}$  and the average effect of the mediating variable given  $\mathbf{X}$  are the same for all  $\mathbf{X}$ . Consider the following parametric family

of violations of assumption (IV-A2):

$$\begin{aligned} E[\theta_{R_i}|\mathbf{X}_i = \mathbf{X}] &= \theta_R + \boldsymbol{\tau}_R^T(\mathbf{X}_i - E[\mathbf{X}]), \\ E[\theta_{M_i}|\mathbf{X}_i = \mathbf{X}] &= \theta_M + \boldsymbol{\tau}_M^T(\mathbf{X}_i - E[\mathbf{X}]). \end{aligned} \quad (7)$$

(IV-A2) is satisfied if  $\boldsymbol{\tau}_R = \mathbf{0}$  and  $\boldsymbol{\tau}_M = \mathbf{0}$ . Suppose we know the value of  $\boldsymbol{\tau}_R$ ,  $\boldsymbol{\tau}_M$  and  $E[\mathbf{X}]$ . Then, we can write,

$$\begin{aligned} Y_i - R_i \boldsymbol{\tau}_R^T(\mathbf{X}_i - E[\mathbf{X}]) - M_i \boldsymbol{\tau}_M^T(\mathbf{X}_i - E[\mathbf{X}]) &= \boldsymbol{\beta}^T \mathbf{X}_i + \theta_R R_i + \theta_M M_i + \epsilon_i, \\ \epsilon_i &= (\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i + (\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i))M_i + Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i) \end{aligned} \quad (8)$$

Now, we show that  $R_i \times \mathbf{X}_i$  are valid IVs for estimating  $\theta_R$  and  $\theta_M$  when the response variable is  $Y_i - \boldsymbol{\tau}_R^T(\mathbf{X}_i - E[\mathbf{X}]) - \boldsymbol{\tau}_M^T(\mathbf{X}_i - E[\mathbf{X}])$ .

**Proposition 2:** Under (7), (IV-A3) and the assumption that  $R$  is randomly assigned, each component of  $R \times \mathbf{X}_i$  is uncorrelated with  $\epsilon_i$ .

**Proof:** Consider a component of  $R \times \mathbf{X}_i$ ,  $RX_{i1}$ . From (8),  $\epsilon_i = (\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i + (\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i))M_i + \{Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i)\}$ . We will prove that  $Cov(RX_{i1}, \epsilon_i) = 0$  by showing that  $RX_{i1}$  is uncorrelated with each of the three summands that make up  $\epsilon_i$ , namely (i)  $Cov(RX_{i1}, (\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i) = 0$ ; (ii)  $Cov(RX_{i1}, (\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i))M_i) = 0$  and (iii)  $Cov(RX_{i1}, Y_i^{(0,0)} - E(Y_i^{(0,0)}|\mathbf{X}_i)) = 0$ . For (i), since  $R_i$  is randomized, we have  $E[(\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i] = 0$  so that  $Cov(R_i X_{i1}, (\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i) = E(R_i X_{i1}(\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i)$ . Furthermore, we have

$$\begin{aligned} E(R_i X_{i1}(\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))R_i) &= E(R_i^2)E(X_{i1}(\theta_{R_i} - E(\theta_{R_i}|\mathbf{X}_i))) \\ &= 0, \end{aligned}$$

where the first equality follows from the fact that  $R$  is randomized and the second equality follows from properties of conditional expectation. This proves (i). For (ii), we first note that

$$\begin{aligned} E[(\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i))M_i] &= E[E[(\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i))M_i|R_i, \mathbf{X}_i]] \\ &= E[E[\theta_{M_i} - E(\theta_{M_i}|\mathbf{X}_i)|R_i, \mathbf{X}_i]E[M_i|R_i, \mathbf{X}_i]] \\ &= 0, \end{aligned}$$

where the second equality follows from (IV-A3) and the third equality follows from the fact that  $R$  is randomized and properties of conditional expectation. Thus,  $Cov(R_i X_{i1}, (\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) M_i) = E(R_i X_{i1} (\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) M_i)$ , and

$$\begin{aligned}
E(R_i X_{i1} (\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) M_i) &= E[E[R_i X_{i1} (\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) M_i | R_i, \mathbf{X}_i]] \\
&= E[R_i X_{i1} E[(\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) M_i | R_i, \mathbf{X}_i]] \\
&= E[R_i X_{i1} E[(\theta_{M_i} - E(\theta_{M_i} | \mathbf{X}_i)) | R_i, \mathbf{X}_i] E[M_i | R_i, \mathbf{X}_i]] \\
&= 0,
\end{aligned}$$

where the third equality follows from (IV-A3) and the fourth equality follows from the fact that  $R$  is randomized and properties of conditional expectation. This proves (ii). For (iii),

$$\begin{aligned}
Cov(R_i X_{i1}, Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]) &= E[R_i X_{i1} \{Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]\}] \\
&= E(R_i) E[X_{i1} \{Y_i^{(0,0)} - E[Y_i^{(0,0)} | \mathbf{X}_i]\}] \\
&= 0,
\end{aligned}$$

where the second equality follows from  $R$  being randomized. This proves (iii).  $\square$

Based on Proposition 2, we can make inferences for  $\theta_R$  and  $\theta_M$  under (IV-A1), (IV-A3) and (7) by replacing  $Y_i$  by  $Y_i - R_i \boldsymbol{\tau}_R^T (\mathbf{X}_i - E[\mathbf{X}]) - M_i \boldsymbol{\tau}_M^T (\mathbf{X} - E[\mathbf{X}])$  in the two stage least squares inference procedure from Section 5. Table 2 shows the results of a sensitivity analysis. The first component of  $\boldsymbol{\tau}_R$  and  $\boldsymbol{\tau}_M$  corresponds to past antidepressant use and the second component corresponds to baseline antidepressant use.

**Dedication.** This paper is dedicated to my friend and mentor Tom Ten Have. Tom provided a lot of insightful suggestions in the early stage of this work, and unfortunately passed away before I could discuss the later stages of the work with him.

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$\tau_R$	$\tau_M$	Direct effect of intervention	Mediator effect
(0,0)	(0,0)	-0.94 (-3.92,2.04)	-2.87 (-8.89, 3.15)
(0.5,0.5)	(0.5,0.5)	-2.28 (-5.26, 0.69)	1.23 (-4.79, 7.24)
(1,1)	(1,1)	-3.63 (-6.69,-0.58)	5.33 (-0.86,11.51)
(-0.5,-0.5)	(-0.5,-0.5)	0.41 (-2.66,3.48)	-6.97 (-13.18,-0.76)
(-1,-1)	(-1,1)	1.76 (-1.48,5.00)	-11.07 (-17.62,-4.51)

Table 2: Estimates for the direct effect of the intervention and the mediator (antidepressant use) effect in the PROSPECT study under different values of the sensitivity parameters  $\tau_R$  and  $\tau_M$ . 95% confidence intervals are in parentheses.

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